

PATENT
USSN 09/432,503
015389-002611US; 018/063c

REMARKS

Claims 41-62 and 65-82 are pending in this application. Claims 41-57 and 74-82 have been allowed, for which applicant is grateful. The other claims stand rejected for issues relating to the practice of the claimed method *in vivo*. The most recent Office Action has been made final.

In this response, some claims are amended, but no new claims have been added. Reconsideration of the application is respectfully requested.

Rejections under 35 USC § 112 ¶ 1:

Claims 58-62 and 65-73 stand rejected under § 112 ¶ 1. The Office Action indicates that the specification is enabled for increasing proliferative capacity of cells *in vitro*, but not *in vivo*. Several reasons are given:

1. The TRT encoding polynucleotide sequence must be operably linked to a promoter (page 4);
2. The target cell must also express telomerase RNA component (page 5);
3. It is important to make sure that telomerization is safe when used in human therapy (page 6);
4. Treating a disease is harder than merely increasing the proliferation of cells associated with the disease (page 7);
5. Knockout animal models are not considered an acceptable model wherein the knocked out gene is reintroduced into the cell (page 12);
6. Telomerase activity in rodent models is significantly different from telomerase activity in humans because rodents have a greater mean telomere length (page 12);
7. The § 1.132 Declaration by Dr. Edward Wirth is not persuasive because the model described is not a proper model for the claimed invention (page 12);
8. Applicants should limit the claims to adenoviral vectors and the specific cell types that can be transduced by adenoviral vectors (page 10).

Answering these issues seriatim:

1. As indicated in the Office Action, "one of skill in the art would be fully aware that . . . the polypeptide must be operably linked to transcriptional control elements". Since the skilled reader would already be *fully aware* of such requirement, there is no need to explicitly indicate

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the requirement for such control elements in the claims¹. Nevertheless, in order to address this point, the claims have now been amended to indicate that the polynucleotide vector *expresses* TRT. Thus, the vector used in the claimed method has all the features necessary to cause TRT to be expressed in the target cell.

2. Even though the telomerase holoenzyme comprises both TRT and the telomerase RNA component, causing expression of telomerase reverse transcriptase is sufficient to increase the proliferative capacity of most human cells. This is because most nucleated mammalian cells constitutively express telomerase RNA component, which makes TRT the rate-limiting component (Bodnar et al., Science. 279:349-52, 1998; C.B. Harley, Oncogene 21:494-502, 2002). Accordingly, it is not necessary to indicate in the claim that the target cell expresses telomerase RNA component.
3. TRT has been extensively studied by laboratories all over the world. There is no direct evidence that it poses a risk when used in therapy. Safety of therapeutic compounds can ultimately only be determined in human clinical trials, which is under the purview of the Food & Drug Administration — not the Patent & Trademark Office².
4. The claims do not require treatment of a disease, only an increase in proliferative capacity of the target cell. Applicants have provided animal models demonstrating that the disclosure is enabling for increasing proliferative capacity for the purpose of treating skin wound and liver cirrhosis. However, without implying any limitation, the user need not be treating a disease in order to practice the claimed invention. The invention is sufficiently enabled by the specification if it provides a way of increasing proliferation of a cell without undue experimentation.

¹ By way of analogy, a skilled artisan reading a patent disclosure for an improved automobile bumper would recognize that the automobile must have a plurality of wheels in order to operate. For this reason, it is unnecessary that the claims indicate that an automobile having such a bumper must also have wheels.

² The Office should not require that an applicant demonstrate that a therapeutic agent is safe or fully effective for humans. See MPEP § 2107.1. "Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The state at which an invention in this field becomes useful is well before it is ready to be administered to humans." *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995).

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5. There is no basis for the assertion that knockout animal models in which the knocked-out gene is reintroduced into the cell is not an acceptable model for gene therapy. This is a value judgment that is unsubstantiated. The Office is requested to withdraw this assertion, or to provide an Examiner's Affidavit explaining the basis for the assertion.³
6. The Office Action cites a paper by Ostler et al. (J. Pediatr. Endocrinol. Metab. 2000;13 Suppl. 6:1467-76) as providing evidence that rodents have longer telomeres than humans. If this is true, then rodent models are in fact *more rigorous* for telomerase therapy, since the expectation of a beneficial or more immediate effect is higher when telomere length is shorter⁴.
7. With due respect, applicants point out that it is improper for the Examiner to dismiss an Expert Declaration out-of-hand⁵. Dr. Wirth goes to great length explaining why the animal model in the Rudolph experiments is a good model for use of TRT in human therapy. The Office has offered no evidence that demonstrates the conclusions of Dr. Wirth are incorrect. Accordingly, the Office should accept that the animal experiments described in the Rudolph paper are a suitable model for telomerase therapy in the manner described by Dr. Wirth.

With respect to limiting the claims to adenovirus and particular target tissues, claim 58 already explicitly indicates that the polynucleotide encoding TRT is an *adenovirus* vector. The Office already agrees that TRT can extend the replicative capacity of cells *in vitro*. Thus, the principal question regarding *in vivo* use is the ability of the adenovirus vector to reach the target cell.

In general, the skilled reader will appreciate that known formulations of adenoviral agents can be applied directly to particular treatment sites *in vivo*, or administered by injection or during surgery. Dependent claims 65-72 explicitly indicate particular target cells. By way of illustration, epithelial cells can be treated topically, by oral administration, or by aerosol; keratinocytes, hair cells, and

³ Applicants are entitled to request an Examiner's Affidavit for evidence that is unsubstantiated and apparently within the personal knowledge of the Examiner. 37 CFR § 1.104(d)(2) and MPEP § 2144.03.

⁴ Page 6 of the Office Action also refers to the Ostler reference as teaching that hTERT halts telomere shortening and is sufficient to prevent senescence in a variety of cell types. This confirms what is taught in the Harley reference, *supra*. It follows that if TRT is successful in increasing proliferative capacity *in vivo* in rodent cells (with their longer telomeres, according to Ostler), then human cells would be at least as easy to treat *in vivo*. Thus, the Ostler reference actually provides additional validation for the rodent model explained in Dr. Wirth's § 1.132 Declaration.

⁵ The PTO should give weight to an expert declaration stating that a person of ordinary skill in the art would have understood the patent specification to describe what is claimed. *In re Alton*, 37 USPQ2d 1578 (Fed. Cir. 1996).

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epithelial cells of the eye can be treated topically; hepatocytes can be treated by direct injection or by administration to the general circulation; cementoblasts and odontoblasts can be treated during dental procedures; osteoblasts and chondrocytes can be treated by direct injection; heart cells can be treated by angioplasty or during surgery; and lymphocytes can be treated by intravenous administration.

Accompanying this Amendment is a compilation of abstracts demonstrating that adenovirus therapy has been used successfully for delivering other genes to such tissues⁶. Claims 65-73 are all limited to use of adenovirus in particular tissues known to be amenable to adenovirus therapy.

Base claim 58 is not limited to a particular tissue. However, as already explained, the use of TRT vectors to increase proliferative capacity according to this invention is a generally applicable technique. Even if there are some tissues that cannot be transduced with adenovirus as required by the claims, generic claims are allowed to read on inoperative embodiments, as long as the user can identify operative embodiments without undue experimentation⁷.

For the invention claimed here, the skilled user may test the adenovirus TRT expression vector for its ability to increase cell proliferative capacity *in vitro*, in accordance with claim 41. Providing there was an administration technique available by which to place the vector in contact with the intended target cell *in vivo* (which would be known in the art), the user could then apply the invention *in vivo*, in accordance with claim 58. This can hardly be viewed as undue experimentation.

Accordingly, use of adenovirus vectors expressing TRT to increase proliferative capacity of the target cells of claims 65-73, and in general as covered by claims 58-62, is enabled by the specification as filed.

⁶ Epithelial cells: Katkin et al., Hum. Gene Ther. 8:171, 1997; Fasbender et al., J. Biol. Chem. 272:6479, 1997; Scaria et al., Gene Ther. 4:611, 1997. Keratinocytes: Lu et al., Proc. Assoc. Am. Physicians 108:165, 1996. Hair cells: Kawamoto et al., Noise Health 3:37, 2001. Hepatocytes: Ilan et al., J. Clin. Invest. 99:1098, 1997. Endothelium: Chen et al., Circ. Res. 80:327, 1997; Miller et al., Mol. Ther. 12:321, 2005. Cementoblasts: Giannobile et al., J. Periodontol. 72:815, 2001. Osteoblasts: Mehrara et al., J. Bone Miner. Res. 14:1290, 1999. Chondrocytes: Ikeda et al., J. Rheumatol. 25:1666, 1998. Cardiomyocytes: Rothmann et al., Gene Ther. 3:919, 1996; Shah et al., Circulation 101:408, 2000. Lymphocytes: Wierda et al., Blood 96:2917, 2000.

⁷ In *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.* 224 USPQ 409 (Fed. Cir. 1984), the patent specification at issue was found to be enabling for the claimed invention even though it listed elements that could form thousands of end products, some of which may not be operative. That some experimentation is necessary does not preclude enablement as long as the amount of experimentation is not unduly extensive. 24 USPQ at 413.

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In the prosecution of this application, applicants have provided two animal model experiments for the use of TRT gene therapy *in vivo* — the rabbit ear model, and the rat liver cirrhosis model. Both these models demonstrate that contacting the target cells *in vivo* with a suitable polynucleotide vector expressing TRT increases proliferative capacity of the cells, in accordance with the claimed invention — and that the increased proliferative capacity has clear therapeutic benefit.

Although applicants believe the specification as filed is fully enabling for the use of TRT for gene therapy *in vitro* or *in vivo* using a range of suitable vectors referred to in the specification, the claims here are modestly limited to the use of adenovirus vector, highlighting a dozen cell types where adenovirus is already recognized as a suitable delivery vehicle.

Withdrawal of this rejection is respectfully requested.

Request for further interview

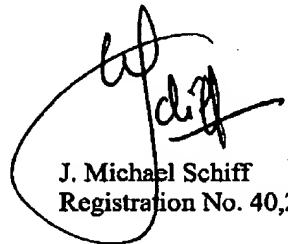
Applicants respectfully request that all outstanding rejections be reconsidered and withdrawn. The application is believed to be in condition for allowance, and a prompt Notice of Allowance is requested.

If after internal review, the Office is still not able to resolve the issue regarding the use of the claimed invention *in vivo*, applicants hereby request a further interview. The Examiner is requested to contact applicants' representative at the telephone number indicated below.

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Should the Patent Office determine that a further extension of time or any other relief is required for further consideration of this application, applicants hereby petition for such relief. The Commissioner is hereby authorized to charge the cost of such petitions and other fees due in connection with the filing of these papers to Deposit Account No. 07-1139.

Respectfully submitted,



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